AWARD NUMBER:	W81XWH-11-1-0553
TITLE:	Mechanisms of Oral Tolerance Breakdown in Food Allergy
PRINCIPAL INVESTIGATOR:	Dr. Talal Chatila
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REPORT DATE:	November 2014
TYPE OF REPORT:	Final Progress Report
PREPARED FOR:	U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012
DISTRIBUTION STATEMENT:	Approved for Public Release; Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
November 2014	Final	30Sep2011 - 31Aug2014

4. TITLE AND SUBTITLE
Mechanisms of Oral Tolerance Breakdown in Food Allergy

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-11-1-0553

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Boston Children's Hospital
Boston, MA 02115-5724

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Aim 1 Th2 and mast-cell mediated suppression of allergen-specific iTR cell response. The hypothesis is that the prevailinign Th2 environment II4raF709 mice suppresses the generation of allergen-specific iTR cells. Blockade of Th2 and mast cell pathways may not only inhibit anaphylaxis but also promote tolerance.
Aim 2 capacity of mast cell depletion to restore oral tolerance in established allergic sensitization. The hypothesis is the mast cell expansion perpetuates oral intolerance to allergen, and that their acute depletion enables tolerance induction in established food allergy. Aim 3 allergen-specific TR cell therapy in the treatment of established oral sensitization. The hypothesis is that allergen-specific iTR cells of WT but not II4raF709 mice would rescue established oral allergic sensitization and suppress the Th-2 skewing and mast cell expansion.

15. SUBJECT TERMS- none provided

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
U	U	U	UU	11	19b. TELEPHONE NUMBER *(include area code)*

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Final Report.

1. Introduction. Our studies have focused on elucidating mechanisms by which oral tolerance is corrupted in food allergy, resulting in the emergence of allergic responses to food allergens. These studies have led to the identification of a critical role for a skewed Th2 environment and mast cell dysregulation in impairing the function of regulatory T cells in food allergy.

2. Keywords: Regulatory T (Treg) cells, food allergy, mast cells, Th2, IgE, Foxp3

3. Accomplishments

3A. Overall Project Summary:

A. Specific Tasks. We have proposed to carry out the following tasks:

Task 1. Th2 and mast-cell mediated suppression of allergen-specifc iTreg cell response. The purpose of this task is to determine mechanisms by which allergic pathways prevent the acquisition of oral tolerance.

Task 2. **Capacity of Mast Cell Depletion to restore oral tolerance in established allergic sensitization.** *The purpose of this task is to determine whether acute mast cell depletion enables the restoration of oral tolerance in mice with established allergic sensitization.*

Task 3. **Allergen-specific Treg cell therapy in the treatment of established oral sensitization**. The purpose of this task is to determine whether allergen-specific iTreg cells of WT, but not *Il4raF709*, mice would rescue established oral allergic sensitization.

3B. Task-specific results:

Task 1 Th2 and mast-cell mediated suppression of allergen-specifc iTreg cell response. The purpose of this task is to determine mechanisms by which allergic pathways prevent the acquisition of oral tolerance.

Task1: Results: Under Task 1, we have proposed to test the hypothesis that the skewed Th2 environment present in the gut of food allergic mice suppresses the development of an effective induced regulatory T (iTreg) cell response, and consequently subverts the induction of oral tolerance to allergens. The *Il4raF709* mice are genetically prone to develop food allergy upon oral sensitization with allergen due to a gain of function mutation in the IL-4 receptor alpha chain (IL-4Rα) [tyrosine (Y) 709 to Phenylalanine (F)] that results in enhanced signaling via the IL-4R. We found that deletion of *Fcerla* in *Il4raF709* mice inhibited anaphylaxis in response oral to ovalbumin (OVA) sensitization, as evidenced by failure to manifest a drop in core body temperature in the sensitized mice in response to OVA challenge (Figure 1 A). consistent with the dependence of the food allergic response in these mice on IgE/mast cells (**Figure 1A**). Other stigmata of allergic sensitization and anaphylaxis, including increased total and OVA-specific IgE, increased release of the mast cell protease 1 (MCP1) into the blood stream upon allergen challenge and small intestinal tissue mastocytosis, were all founbd dependent on intact FceRI expression, as were severely inhibited by concurrent FceRIa deficiency (**Figure 1B-D**). Thus, the mast cells were demonstrated as requisite for the anaphylaxis and, more broadly, for an effective food allergen-directed Th2 response (as reflected by IgE production) in *Il4raF709* mice. Similar results were found for IL-4-deficient *Il4raF709* mice (data not shown). Studies on iTreg cell production revealed that iTreg induction is increased in *Il4raF709/Fcerla* $^{-/-}$ double

mutant mice (**Figure 1E**). Whereas gut CD4$^+$Foxp3$^+$ Treg cells of OVA-sensitized *Il4raF709* mice exhibited evidence of Th2 cell-like reprogramming with increased expression of the transcription factors GATA3 and IRF4 and the cytokine IL-4, associated with Th2 cells, this reprogramming was abolished in *Il4raF709/Fcerla* $^{-/-}$ double mutant mice ((**Figure 1F-H**). These results establish a primary role for mast cell activation in the pathogenesis of in food allergy by virtue of their promotion of the Th2 cell response and suppression of the Treg cell response. The studies shown in Figure 1 have been published in part as Supplementary Figure 5 in the following publication (1): Noval Rivas M, Burton OT, Charbonnier LM, Wise P, Gregoriev P, Oettgen HC, Rachid R, Chatila TA. Regulatory T Cell Reprogramming toward a Th2-Cell-like Lineage Impairs Oral Tolerance and Promotes Food Allergy. Immunity 2015;42(3):512-23. doi: 10.1016/j.immuni.2015.02.004. PubMed PMID: 25769611; PubMed Central PMCID: PMC4366316.

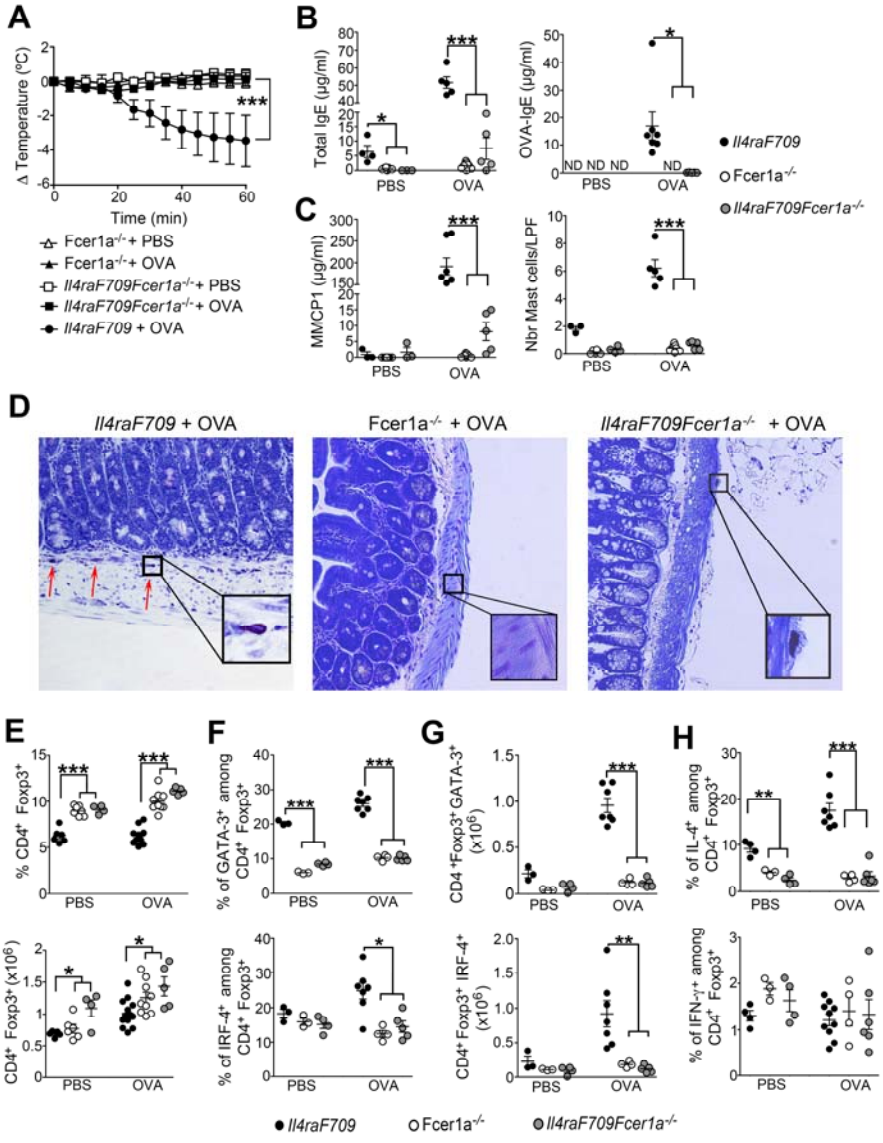

Figure 1. Dysregulated FcεRIα signaling drives the deficiency and Th2 reprogramming of Treg cells in food allergic *Il4raF709* mice. **(A)** Core body temperature changes in PBS and OVA-sensitized *Fcer1a*$^{-/-}$, *Il4raF709* and *Il4raF709Fcer1a*$^{-/-}$ mice following oral challenge with OVA. **(B)** Total and OVA-specific serum IgE concentrations in the respective group post analphylaxis. **(C)** Serum MMCP1 concentrations (left panel) and and intestinal mast cell number (right panel) in the respective mouse group post anaphylaxis. **(D)** Small intestinal histopathology (toluidine blue staining, X200) of PBS and OVA-sensitized *Fcer1a*$^{-/-}$, *Il4raF709* and *Il4raF709Fcer1*$^{-/-}$ mice. Red arrow indicate mast cells. **(E)** Percentages and numbers of CD4$^+$Foxp3$^+$ in the MLN of PBS and OVA-sensitized mouse groups. **(F, G)** Frequencies (**F**) and absolute numbers (**G**) of GATA-3$^+$ and IRF-4$^+$ Treg cells in the respective mouse groups. **(H)** Percentages of Treg cell secreting IL-4 and IFN-γ in the MLN of mice the respective groups. Data are represented as mean ± SEM. N=3-10 mice per group, representative of two independent experiments**.** *p<0.05; **p<0.01; ***p<0.001 by 1 and 2-way ANOVA with post-test analysis.

As part of Task 1, we examined the proposition that Th2 cytokine production by allergen specific Treg cells plays a central role in tolerance breakdown in food allergy, and that their specific deletion in Treg cells prevents food allergy induction in *Il4raF709* mice. Accordingly, we employed *Il4raF709* mice with targeted deletion of both *Il4* and *Il13*, encoding the Th2 cytokines IL-4 and IL-13, respectively, in Treg

cells by using a floxed *Il4-Il13* gene cassette and a Foxp3-directed Cre recombinase (*Il4raF709Foxp3*^{EGFPCre}*Il4-Il13*$^{\Delta/\Delta}$ mice) (**Figure 2A**). Results revealed that compared to *Il4raF709Foxp3*^{EGFPCre} control mice, OVA-SEB-sensitized *Il4raF709Foxp3*^{EGFPCre}*Il4-Il13*$^{\Delta/\Delta}$ mice were protected against anaphylaxis after OVA challenge (**Figures 2B and 2C**). Furthermore, Foxp3-directed deletion of *Il4* and *Il13* corrected the deficit in CD4$^+$Foxp3$^+$ Treg cells in sensitized *Il4raF709* mice and reversed their Th2 cell reprogramming, as assessed by GATA-3 and IRF-4 expression (**Figures 2D and 2E**). It also reduced IL-4 production by Tconv Th2 cells (**Figure 2F**). Collectively, these results indicate that *Il4raF709* Treg cells are reprogrammed to Th2-like cells after oral allergic sensitization and contribute to disease pathogenesis through Th2 cell cytokine expression.

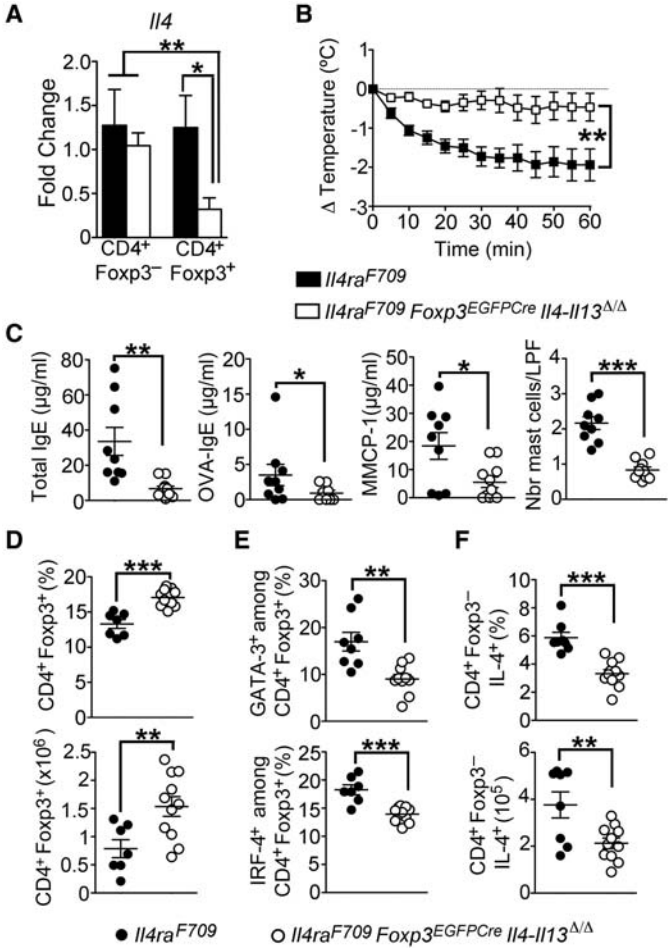

Figure 2. Th2 cell cytokine production by Th2-reprogrammed Treg cells is critical to the food allergic response. A. Real time PCR analysis of *Il4* mRNA transcripts in conventional T (Tconv) cells (CD4$^+$Foxp3$^-$) and regulatory T (Treg) cells (CD4$^+$Foxp3$^+$) sorted from spleens of *Il4ra*^{F709} and *Il4ra*^{F709} *Foxp3*^{EGFPCre}*Il4-Il13*$^{\Delta/\Delta}$. **B.** Core body temperature changes following OVA challenge of OVA-SEB sensitized *Il4ra*^{F709} and *Il4ra*^{F709}*Foxp3*^{EGFPCre}*Il4-Il13*$^{\Delta/\Delta}$ mice. **C.** Serum total IgE, OVA-specific IgE and MMCP-1 concentrations post anaphylaxis of mice from panel (B). **D).**Percentages and numbers of CD4$^+$Foxp3$^+$ Treg cells in the MLN of OVA-SEB-sensitized *Il4ra*^{F709} and *Il4ra*^{F709} *Foxp3*^{EGFPCre} *Il4-Il13*$^{\Delta/\Delta}$ mice. **E.** Frequencies of GATA-3$^+$ or IRF-4$^+$ Treg cells isolated from the MLN of OVA-SEB-sensitized *Il4ra*^{F709} and *Il4ra*^{F709} *Foxp3*^{EGFPCre} *Il4-Il13*$^{-/-}$ mice. **F.** Percentages (top panel) and numbers (bottom panel) of CD4$^+$ Tconv cells producing IL-4 in the MLN of OVA-SEB-sensitized *Il4ra*^{F709} and *Il4ra*^{F709} *Foxp3*^{EGFPCre} *Il4-Il13*$^{\Delta/\Delta}$ mice. Results are representative of 2 independent experiments. N=3-18 mice/group; *p<0.05, **p<0.01 and ***p<0.001 by 1-and 2-way ANOVA with post-test analysis and Student's unpaired two tailed *t* test.

The studies shown in Figure 2 have been published in part as Figure 5 in the following publication (1): Noval Rivas M, Burton OT, Charbonnier LM, Wise P, Gregoriev P, Oettgen HC, Rachid R, Chatila TA. Regulatory T Cell Reprogramming toward a Th2-Cell-like Lineage Impairs Oral Tolerance and Promotes Food Allergy. Immunity 2015;42(3):512-23. doi: 10.1016/j.immuni.2015.02.004. PubMed PMID: 25769611; PubMed Central PMCID: PMC4366316.

Task1: mice used: We have budgeted 240 mice under this task. All budgeted mice under this task have been utilized.

Task 2. **Capacity of Mast Cell Depletion to restore oral tolerance in established allergic sensitization.** *The purpose of this task is to determine whether acute mast cell depletion enables the restoration of oral tolerance in mice with established allergic sensitization.*

Task 2: Results: Under Task 2, we have proposed to either sham sensitize *Il4raF709* and *Il4raF709/Mcpt5-Cre/iDTR* mutant mice or to subject them to oral sensitization with OVA. Subgroups of mice were to be treated with PBS or diphtheria toxin (DT) delivered intraperitoneally (i.p.) concurrently with the oral sensitization In collaboration with Dr. Hans Oettgen at the BCH (co-author on references 1), we found that DT-mediated deletion of mast cells in *Il4raF709/Mcpt5-Cre/iDTR* mice resulted in the suppression of allergic sensitization and the promotion of allergen-specific Treg cell formation (**Figure 3A-D**). In a similar vein, deletion of the tyrosine kinase Syk in mast cells of *Il4raF709* mice using a floxed *Syk* allele also resulted in suppression of the Th2 response (IgE, IL-4) and promotion of the Treg cell response (**Figure 3A-D**). These studies have now been published as Figure 4 in the following publication (2): Burton OT, Noval Rivas M, Zhou JS, Logsdon SL, Darling AR, Koleoglou KJ, Roers A, Houshyar H, Crackower MA, Chatila TA, Oettgen HC. Immunoglobulin E signal inhibition during allergen ingestion leads to reversal of established food allergy and induction of regulatory T cells. Immunity. 2014;41(1):141-51. doi: 10.1016/j.immuni.2014.05.017. PubMed PMID: 25017467; PubMed Central PMCID: PMC4123130.

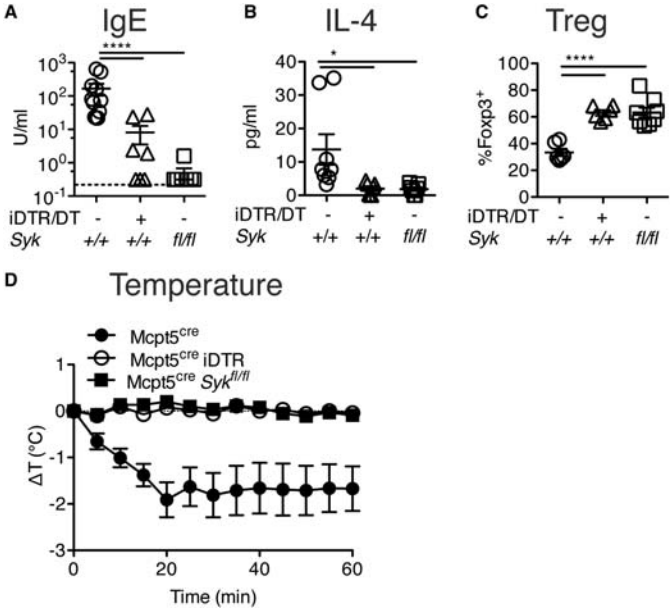

Figure 3. Mast cell depletion or their inhibition by deletion of *Syk* prevents peanut (PN) sensitization. **A**. PN-specific serum IgE levels. Mast-cell-directed induction of the diphtheria toxin receptor (iDTR) or inactivation of *Syk* tyrosine kinase gene in *Il4raF709* mice was achieved by Mctp5^{cre}-driven gene expression. Mice expressing iDTR on mast cells (*Il4raF709* Mcpt5^{cre}iDTR) or with mast-cell-targeted *Syk* deletion (*Il4raF709* Mcpt5^{cre}Syk$^{fl/fl}$) (n = 6–11) were sensitized once a week for 4 weeks with 23 mg PN iby gavage. Mast cells were depleted from Mcpt5cre iDTR mice by i.p. injection of diphtheria toxin over 3 days (100 ng, 500 ng, 500 ng) 1 week prior to initiating PN sensitization (indicated as iDTreg DT "+"). **B**. ELISA analysis of PN-specific IL-4 secretion in splenocyte cultures. **C**. Foxp3^{+} Treg (Treg) cell frequencies among PN-responding CD3ε^{+}CD4^{+} T cells from the MLN. *p<0.05; ****p<0.0001 by 1 -way ANOVA with post-test analysis. **D**. Temperature curves from PN-treated *Il4raF709* mice after enteral challenge with high-dose PN (450 mg). p < 0.001 by repeat measures 2-way ANOVA Mcpt5^{cre} versus Mcpt5cre iDTR and Mcpt5^{cre} versus Mcpt5^{cre}Syk$^{fl/fl.}$

Task 2: mice used: We have budgeted 120 mice under this task. We have used all the budgeted mice.

Task 3. **Allergen-specific Treg cell therapy in the treatment of established oral sensitization**. The purpose of this task is to determine whether allergen-specific iTreg cells of WT, but not *Il4raF709*, mice would rescue established oral allergic sensitization.

Task 3: Results: Decisive progress have been made on Task3 of the proposal, We have now completed this task, showing that allergic sensitization and anaphylaxis in the *Il4RaY709F* mutant mice, which are genetically prone to food allergy, can be prevented by therapy with allergen-specific WT but not *Il4raF709* Treg cells. In the process, we have established the cause of Treg cell failure to control food allergy in I*l4raF709* mice. Our results have been published in two separate reports (1, 3).

To establish whether allergen-specific iTreg cells suppress food allergy, we determined the capacity of OVA-specific iTreg cells to reverse established food allergy in OVA-SEB-sensitized *Il4raF709* mice. WT- or *Il4raF709-DO11.10*$^{+}$*Foxp3*$^{EGFP+}$ iTreg cells were derived that expressed the OVA$_{323-339}$

peptide-specific T cell receptor (TCR) transgene DO11.10 and also carried a Foxp3 reporter allele (*Foxp3*$^{EGFP+}$) to enable identification of Treg cells by virtue of their expression of the enhanced green fluorescent protein (EGFP). WT- or *Il4raF709-DO11.10*$^{+}$*Foxp3*$^{EGFP+}$ iTreg cells were differentiated *in vitro* from naïve CD4^{+} T cells isolated from the respective mouse strain, further purified by cell sorting based on their Foxp3^{EGFP} expression and given intravenously (2.5 x 10^6 cells/mouse) to sensitized *Il4ra*^{F709} mice. The recipient mice were further sensitized for 4 additional weeks and then orally challenged. Administration of a single dose of WT DO11.10^{+} iTreg cells suppressed the anaphylactic response of sensitized *Il4raF709* mice challenged with OVA (**Figure 4A**). This suppression was associated with inhibition of total and OVA-specific IgE responses as well as mast cell expansion and activation, indicative of disease remission (**Figure 4B**). In contrast *Il4ra*^{F709} *DO11.10*$^{+}$*Foxp3*^{EGFP} iTreg cells failed to suppress anaphylaxis or to inhibit the aforementioned disease parameters (**Figures 4A and 4B)**. Transferred WT and *Il4raF709 DO11.10*$^{+}$*Foxp3*^{EGFP} iTreg cells were retrieved at similar numbers in the spleens and MLN of recipient mice, confirming that the *Il4raF709* iTreg cells were functionally defective in suppressing disease (data not shown).

To determine whether defective suppression of oral allergic sensitization was also an attribute of *in vivo*–derived allergen-specific *Il4ra*^{F709} Treg cells, isolated DO11.10^{+} Treg cells from RAG-sufficient WT and *Il4ra*^{F709} *DO11.10*$^{+}$*Foxp3*^{EGFP} mice were employed in a Treg cell transfer model of enforced tolerance (Noval Rivas et al., 2013). WT but not *Il4ra*^{F709} *DO11.10*$^{+}$*Foxp3*^{EGFP} Treg cells were found effective in preventing OVA-induced sensitization and anaphylaxis in *Il4ra*^{F709} mice (**Figures 4C and 3D**). To determine whether Treg cell dysfunction in *Il4raF709* mice resulted from excessive IL-4R/STAT6 signaling, we examined the capacity of Treg cells derived from STAT6-deficient WT and *Il4ra*^{F709} *DO11.10*$^{+}$*Foxp3*^{EGFP} mice to suppress food allergy in sensitized *Il4ra*^{F709} mice. Unlike STAT6-sufficient *Il4ra*^{F709} Treg cells, STAT6-deficient *Il4raF709* Treg cells were equivalent to their WT counterparts in suppressing sensitization and anaphylaxis (**Figures 4C and 4D**). All transferred DO11.10^{+} Treg cell populations were retrieved at similar frequencies and numbers in recipient mice, indicating that the failure of *Il4raF709 DO11.10*$^{+}$*Foxp3*^{EGFP} Treg cells to suppress food allergy reflected an intrinsic functional defect.

The studies shown in Figure 4 below have been published in part as Figure 3 in the following publication (1): Noval Rivas M, Burton OT, Charbonnier LM, Wise P, Gregoriev P, Oettgen HC, Rachid R, Chatila TA. Regulatory T Cell Reprogramming toward a Th2-Cell-like Lineage Impairs Oral Tolerance and Promotes Food Allergy. Immunity 2015;42(3):512-23. doi: 10.1016/j.immuni.2015.02.004. PubMed PMID: 25769611; PubMed Central PMCID: PMC4366316.

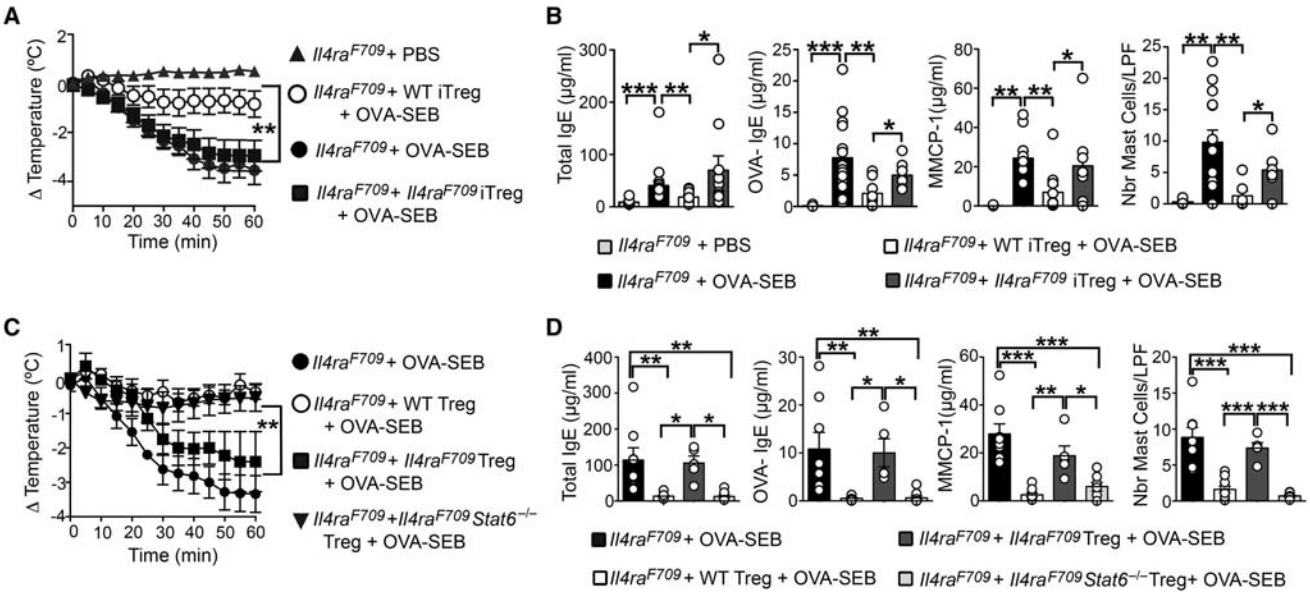

Figure 4. OVA-specific *Il4ra*^{F709} Treg cells fail to suppress food allergy. **A.** Core body temperature changes following OVA challenge of OVA-SEB-sensitized *Il4ra*^{F709} mice that had received *in vitro* generated WT- or *Il4raF709 DO11.10*$^{+}$*Foxp3*^{EGFP} iTreg, as described in Figure S3A. **(B)** Total and OVA-specific serum IgE concentrations, MMCP-1 release and small intestinal mast cell counts in mouse groups shown in panel (A). **(C)** Core body temperature changes following OVA challenge of OVA-SEB-sensitized *Il4ra*^{F709} mice that were either left untreated or given either WT *DO11.10*$^{+}$*Foxp3*$^{EGFP+}$ Treg cells or *Il4raF709DO11.10*$^{+}$*Foxp3*$^{EGFP+}$ STAT6-sufficient or deficient Treg cells. **(D)** Total and OVA-specific serum IgE and serum MMCP-1 concentrations post anaphylaxis of the mouse groups from panel (C). N=5-17 mice per group, pooled from two different experiments. *p<0.05; **p<0.01; ***p<0.001, 1-and 2-way ANOVA with post-test analysis.

Overall, our studies in Figures 2 (Task 1) and Figure 4 (Task 3) establish that Th2 reprogramming of Treg cells results in their failure to enforce oral tolerance in Food allergy, and suggest that measures that overcome such reprogramming such as anti-IgE therapy to suppress mast cell activation (Task 1, Figure 1) or anti-IL-4R therapy may be useful to re-establish tolerance.

Task3: Mice Utilized: We have originally budgeted a total of 180 mice. All the mice budgeted under this task have been utilized.

3C. Key Research Accomplishments:

Our studies, discussed in part in a recent review in the Journal of Allergy and Clinical Immunology, have established the capacity of therapy with allergen-specific Treg cells to prevent and cure food allergy (4). Overall, we have made the following accomplishments:

1. Demonstrated efficacy of immunotherapy for the prevention of food allergy and for curing established food allergy.
2. Identified a profound defect in the capacity of Th2 reprogrammed Treg cells (those carrying the Il4raF709 mutation) to mediate oral tolerance to food allergens.
3. Identified strategies to overcome food allergy in the context of a severely skewed Th2 environment that may reprogram the Treg cells. These include mast cell depletion or neutralization of the Th2 environment with anti-cytokine-cytokine receptor approaches

4. Impact/Conclusions

1) Impact on the development of the principal discipline of the project
   Our studies on experimental murine models of food allergy have established a critical role for impaired Treg cell function in food allergy. These insights will now be carried forward to human clinical studies that investigate the capacity of anti-IL-4/IL-4R antibodies, which neutralize the Th2 environment, to promote tolerance in food allergy.
2) Impact on other disciplines
   Nothing to report
3) Impact on technology transfer
   Nothing to report
4) Impact on society beyond science and technology
   Food allergy is a societal problem in that it affects a large number of individuals, both children and adults, and is associated with significant morbidity as well as fatal episodes of food reactions. Our studies clarify the mechanisms by which food allergy may evolve, and will impact the development of therapies that affect the impact of disease on society.

5. Changes/Problems: Not applicable.

6. Products

6A. Publications

1. Noval Rivas M, Burton OT, Wise P, Charbonnier LM, Georgiev P, Oettgen HC, Rachid R, Chatila TA. Regulatory T Cell Reprogramming toward a Th2-Cell-like Lineage Impairs Oral Tolerance and Promotes Food Allergy. Immunity. 2015;42(3):512-23. doi: 10.1016/j.immuni.2015.02.004. PubMed PMID: 25769611; PubMed Central PMCID: PMC4366316.
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3. Noval Rivas M, Burton OT, Wise P, Zhang YQ, Hobson SA, Garcia Lloret M, Chehoud C, Kuczynski J, Desantis T, Warrington J, Hyde ER, Petrosino JF, Gerber GK, Bry L, Oettgen HC, Mazmanian SK, Chatila TA. A microbiota signature associated with experimental food allergy promotes allergic sensitization and anaphylaxis. J Allergy Clin Immunol. 2013;131(1):201-12. Epub 2012/12/04. doi: 10.1016/j.jaci.2012.10.026. PubMed PMID: 23201093.
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6B. Inventions, Patents and Licenses: Not applicable

6C. Reportable outcomes: See publication list.

6D. Other Achievements: Not applicable.

7. Participants:

Name	Role	Effort
Talal Chatila	PI	1 CM
Louis Marie Charbonnier	Post Doc	8 CM
Magali Noval Rivas	Post Doc	5 CM

8. Special Reporting Requirements: Not applicable

9. Appendices: Not applicable.

References

1. Noval Rivas M, Burton OT, Wise P, Charbonnier LM, Georgiev P, Oettgen HC, Rachid R, Chatila TA. Regulatory T Cell Reprogramming toward a Th2-Cell-like Lineage Impairs Oral Tolerance and Promotes Food Allergy. Immunity. 2015;42(3):512-23. doi: 10.1016/j.immuni.2015.02.004. PubMed PMID: 25769611; PubMed Central PMCID: PMC4366316.
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